Platelet dysfunction associated with ponatinib, a new pan BCR-ABL inhibitor with efficacy for chronic myeloid leukemia resistant to multiple tyrosine kinase inhibitor therapy

Tyrosine kinase inhibitors (TKI) effective for the therapy of chronic myeloid leukemia are known to be associated with defective platelet function. Dasatinib, a potent inhibitor of BCR-ABL1 and SRC family kinases (SFK), is known to cause aberrant platelet function and can induce bleeding, independent of thrombocytopenia.[1] Platelet function abnormalities have been described to a lesser extent with imatinib and bosutinib but these appear not to be affected by nilotinib because of the different spectrum and intensity of inhibition of off-target signaling pathways by the individual TKIs. Here, we describe abnormal platelet function in patients treated with a novel pan BCR-ABL1 inhibitor, ponatinib. Ponatinib is effective in the management of CML resistant to multiple TKIs, as well as having efficacy against the T315I mutation.[2] Analysis of 5 consecutive patients receiving ponatinib showed that all patients had prolonged closure times with PFA 100, a sensitive measure of primary hemostasis.[3]

Patients had received ponatinib for at least two weeks without interruption prior to performing a PFA 100 analysis. The dose intensity varied between 15 mg to 45 mg of ponatinib daily. Only 2 of 5 patients had low platelet counts (64 and 56x10^9/L). None of the patients were on additional anti-platelet therapy or medication implicated in platelet function abnormalities. All 5 patients had prolonged closure times on collagen/epinephrine (>300) and 4 patients had prolonged collagen/ADP closure times (Table 1). Hematocrit values for the 5 patients were all within the normal range (median 0.43%, range 0.38-0.46%). Even allowing for the moderate thrombocytopenia in 2 patients, the marked abnormalities of PFA100 suggest a primary hemostatic defect. No significant bleeding tendencies have been observed in any of the patients so far.

Despite its tolerable side effect profile, ponatinib does have associated side effects due to its activity against other kinases, such as SFK, KIT, VEGFR2, PDGFRα and FGFR1.[2] This interesting and clinically important observation on platelet function could be a result of ponatinib's potent and broad spectrum of multitargeted activity, particularly on PDGFR and SFK. Although the actual mechanism is unknown, ponatinib may affect platelet aggregation by inhibiting key kinases. SFK kinases LYN and FYN play critical roles in early platelet activation by glycoprotein VI, upstream of SYK and PLCγ2.[4,5] The effect of ponatinib on platelet function (prolonging closure times) appears to be independent of its thrombocytopenic effect and also of dose intensity. Not all of the TKIs inhibit platelet function, and these preliminary results advocate the need for vigilance when subjecting patients on ponatinib to any hemostatic challenge.

Table 1. Patients' PFA100 indices on ponatinib therapy.

Patient	Coll/Epi (76-165)	Coll- ADP (60-120)	Platelet count (x10^9/L)
1	>300	107	254
2	>300	158	173
3	>300	147	154
4	>300	255	64
5	>300	263	56

Pratap Neelakantan, David Marin, Mike Laffan, John Goldman, Jane Apperley, and Dragana Milojkovic

Department of Haematology, Imperial College London, Hammersmith Hospital, London, UK.

Correspondence: Dr Dragana Milojkovic, Department of Haematology, Imperial College London, Du Cane Road, London W12 0NN, UK. E-mail: d.milojkovic@imperial.ac.uk

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